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# Should lip dosing be reconsidered when performing open food challenges?

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1 **Title:** Should lip dosing be reconsidered when performing open food challenges?  
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To the Editor,

A lip dose or labial food challenge (LFC) is a simple, easy to perform method of diagnosis that could potentially be a convenient alternative to conducting an oral food challenge in children (1). Rance and Dutau (1) published a paper on LFC in 1997 demonstrating their clinical utility, according to the technique described by Moneret-Vautrin et al. (2). This involved a drop of the allergen being placed on the lower lip and left for 10 seconds to two minutes, with the mouth slightly opened. However, in the study by Rance et al. (1), children with positive LFC did not continue to have an oral food challenge (OFC). A subsequent study by Cantani et al.(3) concluded that the LFC should not replace the OFC, but be used at the first step in a food challenge, particularly where there is a risk of anaphylaxis (4). LFCs are not currently included in international food challenge guidelines (5) (7). Here we present data from lip dose reactions in the Food Allergy and Intolerance (FAIR) study from the Isle of Wight in the United Kingdom (UK), with the aim of demonstrating the predictive value of LFCs for diagnosis of food allergy, compared to OFCs.

## **Methodology**

The FAIR study comprised of two different types of cohorts: The FAIR birth cohort (n = 969) which was seen and challenged at 1, 2, 3, and 10/11 years of age (7–9). The FAIR school cohorts included 3 cohorts of children aged 6, 11 and 15 years (n = 798, 775 and 757 respectively) (8,11). In the FAIR birth cohort, 900 (92.9%), 858 (88.5%), 891 (92.0%) and 827 (85.4%) children were seen at 1, 2, 3, and 10/11 years of age respectively. In the FAIR school cohorts, 798 (55.4%), 775 (47.4%) and 757 (50.2%) children were seen at 6, 11 and 15 years of age respectively. Recruitment of participants and data collection has been previously described in detail elsewhere (8,10).

Children were clinically examined and skin prick tests (SPT) were performed to common food allergens (milk, egg, cod, sesame, wheat and peanut) and invited for food challenges when indicated. A positive SPT was defined by a mean wheal diameter of 3 mm or greater than the negative control (saline). SPT was conducted using standardised allergen reagents and methodology (ALK-Abello, Hørsholm, Denmark). Eczema was measured using the question “Has your child ever been diagnosed with eczema”.

The labial dose was performed by rubbing the inner lower lip five times with a cooked sample of the allergenic food. In order to prevent irritant reactions, only plain foods were used (e.g. unsalted rather than salted peanuts). The challenge outcomes were graded according to the Isle of Wight David Hide Asthma and Allergy Research Centre protocols and later those of the PRACTALL guidelines (6), which were very similar.

For the 10 year follow-up of the FAIR birth cohort, ethical approval for the study was obtained from the NRES South Central – Southampton B Research Ethics Committee (ref: 10/H0504/11). For all other cohorts, ethical approval was obtained from the Isle of Wight, Portsmouth, and South East Hampshire Local Research Ethics Committee (ref: 09/01).

## Results

### Initial analyses

The demographic data for the full cohorts has previously been published in a number of prevalence papers from the Isle of Wight (7–10). A total of 112 LFCs took place. This included four cases of children with positive LFCs, who did not proceed to an OFC, as parents declined to continue with the process. Therefore a total of 108 LFCs, followed up by an open food challenge, were included in the primary analysis, as indicated in Figure 1.

Of these 108 LFCs, a positive labial reaction was noted in nine challenges. All nine positive labial reactions resulted in a positive oral food challenge. Looking overall at the 108 food challenges, of which nine were preceded by a positive LFC, we have calculated a positive predictive value of 100% (95% CI 66.4-100%), a negative predictive value of 72.7% (95% CI 68.8-76.3), with 100% specificity (95% CI 94.9-100) and 25.0% sensitivity (95% CI 12.1-42.2).

The nine positive labial reactions, summarised in Table 1, were to sesame (n=1), peanut (n=3), prawn (n=1) and egg (n=4). The most common reaction to the labial dose was urticaria (n = 3), followed by lip angioedema (n =2). Other symptoms reported were rash and rhinorrhea. The dose reacted to during OFC varied from 250mg for peanut and egg (equating to 62.5 mg peanut and 32.5mg egg protein respectively) to a maximum eliciting dose of 40g prawn (equating to 1000mg prawn protein). The majority of participants reacted within the first 3 challenge doses (250mg, 500mg and 1g), apart from the participant who reacted to 40g of prawn.

Overall 44 children (40.7%) reported a history of eczema. 55.6% (n = 5) of those with a positive LFC had a history of eczema, compared to 39.8% (n = 39) of those with a negative LFC, however this difference was not statistically significant (Fisher's exact test p = 0.483). In terms of sensitization, 77.8% (n = 7) of those with a positive LFC had a positive SPT, compared to 47.6% (n = 39) of those with a negative LFC, however this difference was not significantly different (Fisher's exact test p = 0.158).

### Additional analyses

We conducted additional analyses including the four cases of children with positive LFCs, who did not proceed to an OFC. Hypothetically if these four participants had a positive OFC result, the positive predictive value of the LFC would remain at 100% (95% CI 75.29-100), as would the negative predictive value of 72.7% (95% CI 68.8-76.3) and the specificity of 100% (95% CI 95.01-100). However the sensitivity would increase to 32.5% (95% CI 18.57-49.13). Conversely if these four participants had a negative OFC result, the positive predictive value would decrease to 69.2% (95% CI 42.6-87.2), the negative predictive value would remain stable at 72.7% (95% CI 68.8-76.3), as would the sensitivity remaining at 25% (95% CI 12.1-42.2). However the specificity would decrease to 94.7% (95% CI 87.1-98.6).

## Discussion

This study aimed to investigate whether a lip dose challenge can be used as a feasible alternative to a complete oral food challenge protocol in children. The data shows that a positive LFC was highly indicative of a positive oral food challenge, but a negative LFC does not rule out a positive oral food challenge. Although proportionately more children with a positive LFC had both eczema and a positive SPT to the food, compared to children with a negative LFC, the difference was not statistically significant. Due to the small number of children with a positive labial challenge, our analysis may be underpowered, so results should be interpreted with caution.

Unlike the study of Rance et al.,(1) where 4.5% of cases experienced systemic reactions, none of the children in this study experienced systemic reactions. This suggests, using our limited data, that a lip dose challenge is both safe and feasible. In this dataset, there were four cases of positive LFCs that did not proceed to a full OFC due to lack of parental consent to proceed. It was not possible to include these four cases in the statistical analysis, as we could not compare them against a valid OFC outcome and it is not possible to predict whether a systemic reaction would have occurred. Unfortunately there is limited published research available to compare our findings to. The only other study we could find referring to the usefulness of the labial challenge is that of Cantani et al. (3), who conducted 113 OFCs in children, the majority to cows' milk.

As ours was an observational birth cohort study, rather than a sample recruited from a clinical setting, we could not determine a priori which food allergens to investigate. We observed positive LFCs to only four different foods: sesame, peanut, shellfish and egg. Although cows' milk is the most common food allergen in young children in the United Kingdom (8,11), the sample included in this study did not include any positive LFCs to cows' milk. This is probably because most CMA in the UK is non-IgE mediated as indicated in the UK cohort of the FAIR study in 2006 (12) and then confirmed by the of the EUROPREVALL study (13). Rance et al. (1) included LFCs to a wider variety of foods (mustard, cod, kiwi, snails, fennel and duck); which is reflective of the differing prevalence of food allergies between the UK and France.

The strengths of this study are that it included children of varied ages, using standardized protocols. The main limitation of the study is the small sample size of children with a positive LFC, which included only four food allergens. In conclusion our data, despite a very limited dataset, indicates that LFCs are feasible and safe. A positive LFC is highly indicative of a positive OFC, but a negative LFC does not rule out a positive OFC. This may have implications for implementation of food challenges in clinics with limited resources, particularly in terms of indicating which children are more likely to have a positive OFC.

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147 **Conflicts of interest:** The authors declare no conflicts of interest.

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Table 1 Summary of challenges undertaken at different ages

Age	Sex	Foods challenged	Number participants with eczema	Number of positive SPTs	Number of LFCs	Number of positive LFCs	Number of positive OFC following positive LFC	Number of negative LFCs	OFC outcome following negative LFC
1 year	27 male 13 female	Milk, egg, cod, wheat, corn, tomato, citrus fruit, strawberry	16	13	40	3 (egg)	3	37	10 positive 27 negative
2 years	6 male 4 female	Milk, egg, wheat, citrus fruit	9	4	10	1 (egg)	1	9	2 positive 7 negative
3 years	14 male 8 female	Egg, cod, corn, peanut, sesame, kiwi, pineapple	11	10	22	1 (peanut)	1	21	4 positive 17 negative
6 years	5 male 4 female	Sesame, banana, peanut, cod, almond	3	9	9	0	0	9	2 positive 7 negative
10 years	6 male 2 female	Peanut, egg, brazil nut	3	6	8	0	0	8	4 positive 4 negative
11 years	4 male 7 female	Peanut, almond, sesame, soy, cheese	1	8	11	2 (peanut)	2	9	2 positive 7 negative
15 years	5 male 3 female	Milk, fruit, soya, hazelnut, prawn, sesame, raisin	1	3	8	2 (1 child sesame & 1 child prawn)	2	6	3 positive 3 negative
<b>Total</b>	<b>67 male 41 female</b>		<b>71</b>	<b>53</b>	<b>108</b>	<b>9</b>	<b>9</b>	<b>99</b>	<b>27 positive 72 negative</b>

SPT: Skin prick test OFC: Oral food challenge. LFC: Labial food challenge.

Figure 1. Flowchart outlining number of participants with positive and negative results

